Pharmaceutical Compositions & Devices for Dispensing the Same

The present invention relates to dry powder pharmaceutical compositions comprising a benzodiazepine for administration by inhalation, and in particular, benzodiazepine dry powder compositions and inhaler devices for dispensing the same.

Benzodiazepines are sedative-hypnotic agents that were first introduced in 1960. They are commonly used for a variety of situations that include seizure control, anxiety, alcohol withdrawal, insomnia, control of drug-associated agitation, as muscle relaxants, and as preanesthetic agents. They also are combined frequently with other medications for conscious sedation before procedures or interventions. Because of their widespread popularity, these drugs can be abused. In addition, they are also known to be used in overdose, either alone or in association with other substances.

The most widely used benzodiazepines include clobazam, clonazepam, diazepam, lorazepam and midazolam. Any benzodiazepines may be employed in the present invention, including these well-known benzodiazepines, as well as less common ones.

Clobazam is a 1,5 benzodiazepine having the chemical name 7-chloro-1,5-dihydro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3H)-dione. Clonazepam is a 1,4 benzodiazepine having the chemical name 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one. Diazepam has the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Lorazepam has the chemical name 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one and midazolam has the chemical name 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine.

In the compositions of the present invention, the benzodiazepine is preferably either clobazam or clonazepam. Clobazam is particularly preferred because, based upon the available literature, it is believed that this benzodiazepine exhibits fewer

side effects tham other benzodiazepines. See, for example, Trimble et al, Benzodiazepines, page 5 (2000). Moreover, it is believed that the side effects will be further reduced when clobazam is delivered to the lungs via inhalation.

At present, commercially available benzodiazepines are generally formulated for administration by intravenous injection or for rectal administration, especially when intended for treating epilepsy. Both of these modes of administration are clearly inconvenient in certain circumstances and unpleasant for the patient.

Some oral benzodiazepine formulations are available, usually in the form of tablets. However, the oral formulations suffer from the draw back that they require significantly greater doses of the benzodiazepine in order to achieve the same effect as the intravenous injections or rectally administered formulations. For example, Rivotril (clonazepam) is used to treat epilepsy and comes as an intravenous injection or oral tablets. The recommended dose of benzodiazepine when taking the tablets is 4-8mg per day, compared to the 1mg intravenous injection. What is more, oral dosing suffers from the disadvantage that there is a relatively long delay between administration and the onset of the therapeutic effect. First pass metabolism of the benzodiazepine is also an issue.

Although other modes of administering benzodiazepines have been proposed, these have met with limited success. Transmucosal nasal administration of benzodiazepine has been described in WO 90/02737 (Goldberg), in particular for improving sleep. Where sleep is to be induced, it is clearly desirable for the therapeutically active agent to have a rapid effect upon administration and it is disclosed that compositions including solutions, suspensions, ointments, and gels, containing a benzodiazepine can provide a hypnotic effect of improved duration and which is more efficiently and precisely controlled, compared to conventional modes of administration. US Patent No. 6,627,211 (SK Corporation) discloses a composition for transmucosal nasal administration. In particular, the patent discloses the coadministration of a medicament, such as a benzodiazepine, with a pharmaceutically acceptable co-solvent system comprising an aliphatic alcohol, a glycol, and water, and their combinations with a biological surfactant such as a bile

salt or a lecithin. The aqueous co-solvent system is said to control and promote the rate and extent of transmucosal permeation and absorption of the active agent.

However, nasal administration is not very pleasant for the patient, especially when regular administration is required over a period of time. Caking within the nasal cavity can occur, causing discomfort. This route of administration also suffers from the problem than only a limited volume of the benzodiazepine formulation can be administered. Above this, the formulation will actually be swallowed and has little or no therapeutic effect.

The administration of compositions comprising benzodiazepine by inhalation has also been contemplated. US Patent No. 5,457,100 (Daniel) discloses treatments for panic disorders and seizure disorders, wherein compositions comprising a benzodiazepine are inhaled. The treatment is primarily envisaged as an emergency treatment and the dose of benzodiazepine is delivered to the patient without too much accuracy. The compositions comprise a propellant and are dispensed using conventional devices, such as aerosolised metered dose pumps, manual metered dose pumps and metered dose spray-producing squeeze bottles.

WO 02/094244 (Alexza Molecular Delivery Corporation) discloses inhalation of a benzodiazepine in the form of an aerosol formed by heating a composition containing the benzodiazepine to form a vapour and subsequently allowing the vapour to condense into an aerosol. Such a condensation aerosol requires an inhalation device which has at least three elements, namely an element for heating the composition to form a vapour, an element allowing the vapour to cool, and an element allowing the aerosol thereby formed to be inhaled. It is alleged that this composition and mode of administration rapidly produces a peak plasma concentration of the benzodiazepine. However, this laborious method of producing an aerosol is relatively unreliable and the amount of benzodiazepine actually dispensed in a dose is unpredictable, which can lead to over- or underdosing, both of which are clearly undesirable and can pose a dangerous risk to the patient's health.

It is believed that inhalable benzodiazepine dry powder compositions according to the invention will achieve a therapeutic effect within 15 minutes of administration. This is a significantly faster time to therapeutic effect than that achieved when benzodiazepine compositions are administered orally or rectally.

Moreover, benzodiazepines are known to have a relatively high first pass metabolism and the resulting metabolites are less effective therapeutically than the benzodiazepines themselves. By administering benzodiazepines via the pulmonary route, much more of the unmetabolised drug is delivered systemically. This should allow the benzodiazepine to be administered in smaller doses than is typically required via the oral or rectal routes. For example, in Medhndiratta et al, "Clobazam monotherapy in drug naïve adult patients with epilepsy", 12 Seizures 226-228 (2003), a study of 26 patients showed an average daily dose of 26.86mg of clobazam, with a range of 20mg to 80mg. In Trimble et al, "Benzodiazepines" at page 69, doses of 10mg every 6-8 hours are mentioned.

The above discussed characteristics of the inhalable clobazam compositions of the present invention, in combination with clobazam's relatively low incidence of adverse drug interaction, also make it particularly suitable for adjunctive therapy, that is, for use in combination with other medications, such as other seizure medications. In accordance with some embodiments of the present invention, compositions for adjunctive therapy are provided, comprising a primary drug in combination with an adjunctive drug, the adjunctive drug including a benzodiazepine, preferably clobazam, administered by inhalation. The primary drug may be carbamazepine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, piracetam, primidone, tigabine, topiramate, valproate, vagabatrin, acetazolmide, adrenocorticotropic hormone, mephytoin, mesuximide, nitrazepam and pharmaceutically acceptable salts thereof.

Patients taking oral medication for seizure disorders take these medications over a relatively long period of time (for example, over a few days) during periods when they are more likely to experience seizures. Due to the relatively slow time to

therapeutic effect of these oral medications, the patient cannot afford to wait until a triggering event occurs, such as an event which is likely to trigger a seizure, to take the medication. In contrast, with the pulmonary administration of benzodiazepines (and of clobazam in particular), it is believed that a much faster time to therapeutic effect can be achieved, thereby allowing the patient to take the medication much less frequently. This is a significant advantage because benzodiazepines exhibit side effects and it is believed that with the less frequent dosing required via inhalation, these side effects can be reduced. With clobazam, which already exhibits fewer side effects than other benzodiazepines, the further reduction in the frequency of dosing, in combination with the lower dosages, are believed to make an inhalable formulation particularly advantageous.

Another advantage of pulmonary administration of benzodiazepines for the treatment of seizure disorders is that it does not require the dose to travel through the digestive system of the patient. This is significant because, during a seizure, the digestive process of the patient may be disrupted. Therefore, even if a patient successfully swallows the oral medication just prior to a seizure, the seizure itself may actually prevent the medication from being digested and therefore from having its desired therapeutic effect. In contrast, as long as a patient is able to successfully inhale an inhalable benzodiazepine formulation, the drug should be absorbed systemically.

Pulmonary inhalation is also more socially acceptable to patients than rectal or intramuscular administration. Intramuscular administration involves injection, which is uncomfortable for many patients and for children in particular. Rectal administration is also inconvenient and uncomfortable. Moreover, many seizure patients are children who may require administration of their medication whilst at school. School personnel may be reluctant to give rectal doses or to provide injections. Even nasal administration has its disadvantages, often leading to caking within the nasal cavity and discomfort to the patient.

Thus, according to a first aspect of the present invention, a pharmaceutical composition comprising benzodiazepine is provided, for administration by

inhalation. In one embodiment of the invention, the composition is a dry powder composition. In another embodiment of the invention, the composition is suitable for pulmonary inhalation.

According to another aspect of the present invention, the pharmaceutical compositions comprising benzodiazepine are for use in therapy. In particular, the compositions are for treating epilepsy. The compositions are useful for treating seizures in general, including partial and acute repetitive seizures. The compositions may also be used to treat the condition called Status Epilepticus. The term status epilepticus may be used to describe any continuing type of seizure. The compositions may also be used to treat Acute Panic Disorder. The compositions according to the present invention may also be used as a sedative or as premedication (pre-operative medication).

In another embodiment of the present invention, the composition is not for use in treating seizure disorders or panic disorders.

The inhalable compositions of the present invention may be dispensed using either pressurised metered dose inhalers (pMDIs) or dry powder inhalers (DPIs).

Pressurised metered dose inhalers typically have two components. Firstly, there is a canister component in which the drug particles (in this case a benzodiazepine) are stored under pressure in a suspension or solution form. Secondly, there is a receptacle component used to hold and actuate the canister. Typically, a canister will contain multiple doses of the formulation, although it is possible to have single dose canisters as well. The canister component typically includes a valved outlet from which the contents of the canister can be discharged. Aerosol medication is dispensed from the pMDI by applying a force on the canister component to push it into the receptacle component thereby opening the valved outlet and causing the medication particles to be conveyed from the valved outlet through the receptacle component and discharged from an outlet of the receptacle. Upon discharge from the canister, the medication particles are "atomised", forming an aerosol. It is intended that the patient coordinate the discharge of aerosolised medication with

his or her inhalation, so that the medication particles are entrained in the patient's inspiratory flow and conveyed to the lungs. Typically, pMDIs use propellants to pressurise the contents of the canister and to propel the medication particles out of the outlet of the receptacle component. In pMDIs, the formulation is provided in liquid form, and resides within the container along with the propellant. The propellant can take a variety of forms. For example, the propellant can comprise a compressed gas or liquefied gas.

In a dry powder inhaler, the dose to be administered is stored in the form of a non-pressurised dry powder and, on actuation of the inhaler, the particles of the powder are inhaled by the patient. Dry powder inhalers can be "passive" devices in which the patient's breath is the only source of gas which provided a motive force in the device. Alternatively, in "active" devices, a source of compressed gas is used. The dry powder compositions according to the present invention may be dispensed using an active or a passive DPI. Examples of passive inhaler devices include Rotahaler and Diskhaler (GlaxoSmithKline) and the Turbohaler (Astra-Draco). Examples of active inhalers include the inhaler marketed under the name Inhance™ by Nektar Therapeutics and used in their Exubera™ product providing inhaled insulin, and Vectura Limited's Aspirair™ device. A particularly preferred active dry powder inhaler is described in more detail below.

In a preferred embodiment, the dose of the composition of the present invention required to provide the desired therapeutic effect will contain from about 0.25mg to about 20mg of a benzodiazepine or a pharmaceutically acceptable salt thereof. Preferably, the dose comprises from about 0.5mg to about 10mg. Even more preferably, the dose will comprise from about 1mg to about 7mg, and most preferably from about 2mg to about 3mg of said benzodiazepine.

In a particularly preferred embodiment of the present invention, a dry powder composition comprising a benzodiazepine is provided, having a good dosing efficiency. This, in combination with the advantages afforded by pulmonary administration of a dry powder formulation, allows the benzodiazepine to be

administered in smaller doses than required when using the currently available compositions and modes of administration.

The dosing efficiency is achieved by optimising the dry powder composition comprising the benzodiazepine, and/or the device used to dispense the composition.

Good dosing efficiency will have a large number of benefits. For example, as it is possible to repeatedly and reliably deliver a higher proportion of the active agent in a dose, it will be possible to reduce the size of the doses whilst still achieving the same therapeutic effect. This is clearly very attractive.

The lower dose and the high reproducibility achieved by embodiments of the present invention means that the therapeutic effect achieved by a given dose will be more predictable and consistent. This obviates the risk of having an unexpected and unusually high dosing efficiency with the conventional devices and powders, which could lead to an undesirably high dose of active agent being administered, effectively an overdose.

Furthermore, high doses of therapeutically active agents has long been linked with the increased incidence of undesirable side effects. Thus, the present invention may help to reduce the incidence of side effects by reducing the dose administered to all patients.

Naturally, the reduction in the amount of an active agent required to achieve the same therapeutic effect is attractive because of the cost implications. However, it is also likely to be deemed much safer by regulatory bodies such as the FDA in the United States.

The metered dose (MD) of a dry powder formulation is the total mass of active agent present in the metered form presented by the inhaler device in question. For example, the MD might be the mass of active agent present in a capsule for a Cyclohaler (trade mark), or in a foil blister in an Aspirair (trade mark) device.

The emitted dose (ED) is the total mass of the active agent emitted from the device following actuation. It does not include the material left inside or on the surfaces of the device. The ED is measured by collecting the total emitted mass from the device in an apparatus frequently identified as a dose uniformity sampling apparatus (DUSA), and recovering this by a validated quantitative wet chemical assay.

The fine particle dose (FPD) is the total mass of active agent which is emitted from the device following actuation which is present in an aerodynamic particle size smaller than a defined limit. This limit is generally taken to be 5μm if not expressly stated to be an alternative limit, such as 3μm or 1μm, etc. The FPD is measured using an impactor or impinger, such as a twin stage impinger (TSI), multi-stage impinger (MSI), Andersen Cascade Impactor or a Next Generation Impactor (NGI). Each impactor or impinger has a pre-determined aerodynamic particle size collection cut points for each stage. The FPD value is obtained by interpretation of the stage-by-stage active agent recovery quantified by a validated quantitative wet chemical assay where either a simple stage cut is used to determine FPD or a more complex mathematical interpolation of the stage-by-stage deposition is used.

The fine particle fraction (FPF) is normally defined as the FPD divided by the ED and expressed as a percentage. Herein, the FPF of ED is referred to as FPF(ED) and is calculated as FPF(ED) = (FPD/ED) x 100%.

The fine particle fraction (FPF) may also be defined as the FPD divided by the MD and expressed as a percentage. Herein, the FPF of MD is referred to as FPF(MD), and is calculated as FPF(MD) = (FPD/MD) x 100%.

The FPF(MD) can also be termed the 'Dose Efficiency' and is the amount of the dose of the pharmaceutical dry powder formulation which, upon being dispensed from the delivery device, is below a specified aerodynamic particle size.

It is well known that particle impaction in the upper airways of a subject is predicted by the so-called impaction parameter. The impaction parameter is defined

as the velocity of the particle times the square of its aerodynamic diameter. Consequently, the probability associated with delivery of a particle through the upper airways region to the target site of action, is related to the square of its aerodynamic diameter. Therefore, delivery to the lower airways, or the deep lung is dependant on the square of its aerodynamic diameter, and smaller aerosol particles are very much more likely to reach the target site of administration in the user and therefore able to have the desired therapeutic effect.

Particles having aerodynamic diameters in the range of 5μm to 2μm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 3 to 0.05μm are likely to be deposited in the alveoli. So, for example, high dose efficiency for particles targeted at the alveoli is predicted by the dose of particles below 3μm, with the smaller particles being most likely to reach that target site.

For formulations to reach the deep lung or the blood stream via inhalation, the active agent in the formulation must be in the form of very fine particles, for example, having a mass median aerodynamic diameter (MMAD) of less than 10μm. It is well established that particles having an MMAD of greater than 10μm are likely to impact on the walls of the throat and generally do not reach the lung. Particles having an MMAD in the region of 5μm to 2μm will generally be deposited in the respiratory bronchioles whereas particles having an MMAD in the range of 3 to 0.05μm are likely to be deposited in the alveoli or be absorbed into the bloodstream.

Thus, in a preferred embodiment of the present invention, for delivery to the lower respiratory tract or deep lung, the MMAD of the active particles is not more than 10μm, and preferably not more than 5μm, more preferably not more than 3μm, and may be less than 1μm. Ideally, at least 90% by weight of the active particles in a dry powder formulation should have an MMAD of not more than 10μm, preferably not more than 5μm, more preferably not more than 3μm and most preferably not more than 2μm.

When dry powders are produced using conventional processes, the active particles will vary in size, and often this variation can be considerable. This can make it difficult to ensure that a high enough proportion of the active particles are of the appropriate size for administration to the correct site. It is therefore desirable to have a dry powder formulation wherein the size distribution of the active particles is as narrow as possible. This will improve dose efficiency and reproducibility.

The compositions of the present invention are preferably formulated to reduce the loss of the pharmaceutically active agent, so that a high dosing efficiency can be achieved. By loss of the pharmaceutically active agent, it is meant that the active agent is not dispensed by the delivery device, or it is not dispensed in a manner that will result in it reaching the lower respiratory tract or deep lung, where the active particles should be deposited in order to have their desired therapeutic effect.

In particular, the agglomeration of the fine particles in the composition leads to loss of the active agent. The fine particles of active agent tend to agglomerate and if these agglomerates are not broken up upon actuation of the dispensing device, the active agent particles will not reach the desired part of the lung. It has been found that the deagglomeration of the fine powder particles can be greatly enhanced by the addition of force control agents which reduce particle cohesion to allow agglomerates to break up more easily, as well as by the methods used to prepare the particles.

Fine particles, that is, those with an MMAD of less than 10μm, are thermodynamically unstable due to their high surface area to volume ratio, which provides a significant excess surface free energy and encourages the particles to agglomerate. In the inhaler, agglomeration of fine particles and adherence of such particles to the walls of the inhaler are problems that result in the fine particles leaving the inhaler as large, stable agglomerates, or being unable to leave the inhaler and remaining adhered to the interior of the inhaler, or even clogging or blocking the inhaler.

The uncertainty as to the extent of formation of stable agglomerates of the particles between each actuation of the inhaler, and also between different inhalers and different batches of particles, leads to poor dose reproducibility. Furthermore, the formation of agglomerates means that the MMAD of the active particles can be vastly increased, with agglomerates of the active particles not reaching the required part of the lung.

The tendency of fine particles to agglomerate means that the FPF of a given dose is highly unpredictable and a variable proportion of the fine particles will be administered to the lung, or to the correct part of the lung, as a result.

In an attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include additive material.

The additive material is intended to decrease the cohesion between particles in the dry powder formulation. It is thought that the additive material interferes with the weak bonding forces between the small particles, helping to keep the particles separated and reducing the adhesion of such particles to one another, to other particles in the formulation if present and to the internal surfaces of the inhaler device. Where agglomerates of particles are formed, the addition of particles of additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on actuation of the inhaler device, whereupon the particles are expelled from the device and inhaled. As the agglomerates break up, the active particles return to the form of small individual particles which are capable of reaching the lower lung.

In the prior art, dry powder formulations are discussed which include distinct particles of additive material (generally of a size comparable to that of the fine active particles). In some embodiments, the additive material may form a coating, generally a discontinuous coating, on the active particles and/or any carrier particles.

Preferably, the additive material is an anti-adherent material and it will tend to reduce the cohesion between particles and will also prevent fine particles becoming attached to the inner surfaces of the inhaler device. Advantageously, the additive material is an anti-friction agent or glidant and will give better flow of the pharmaceutical composition in the inhaler. The additive materials used in this way may not necessarily be usually referred to as anti-adherents or anti-friction agents, but they will have the effect of decreasing the cohesion between the particles or improving the flow of the powder. The additive materials are often referred to as force control agents (FCAs) and they usually lead to better dose reproducibility and higher fine particle fractions.

Therefore, an FCA, as used herein, is an agent whose presence on the surface of a particle can modify the adhesive and cohesive surface forces experienced by that particle, in the presence of other particles. In general, its function is to reduce both the adhesive and cohesive forces.

In general, the optimum amount of additive material to be included in a dry powder formulation will depend on the chemical composition and other properties of the additive material and of the active material, as well as upon the nature of other particles such as carrier particles, if present. In general, the efficacy of the additive material is measured in terms of the fine particle fraction of the composition.

Known additive materials usually consist of physiologically acceptable material, although the additive material may not always reach the lung. For example, where the additive particles are attached to the surface of carrier particles, they will generally be deposited, along with those carrier particles, at the back of the throat of the user.

Thus, in a preferred embodiment of the present invention, the composition further comprises an additive material.

Preferred additive materials for use in dry powder formulations include amino acids, peptides and polypeptides having a molecular weight of between 0.25 and 1000 kDa

and derivatives thereof, dipolar ions such as zwitterions, phospholipids such as lecithin, metal stearates such as magnesium stearate, sodium stearyl fumate or colloidal silicon dioxide.

In an embodiment of the present invention, the dry powder compositions may include one or more FCAs in an amount form about 0.1% to about 40% by weight, preferably from about 0.15% to 10% by weight, more preferably from about 0.2% to about 5% by weight, and most preferably from about 0.5% to about 2% by weight.

When the FCA is an amino acid or a phospholipid, it is preferably provided in an amount form about 0.1% to about 10% by weight, more preferably about 0.5% to about 5% by weight, and most preferably about 2% by weight. Preferably, at least 95% by weight of the micronised amino acid or phospholipid has a particle diameter of less than 150μm, preferably less than 100μm and most preferably less than 50μm.

Where the FCA is a metal stearate or sodium stearyl fumarate, it is preferably provided in an amount from about 0.05% to about 10%, more preferably from about 0.15% to about 2%, and most preferably from about 0.15% to about 0.5%, by weight.

Where reference is made to particle size of particles of the dry powder formulation, it is to be understood that, unless indicated otherwise, the particle size is the volume weighted particle size. The particle size may be calculated by a laser diffraction method. Where the particle also includes an indicator material on the surface of the particle, advantageously the particle size of the coated particles is also within the preferred size ranges indicated for the uncoated particles.

In certain embodiments of the present invention, the benzodiazepine formulation is a "carrier free" formulation, which includes only the benzodiazepine and one or more additive materials. In accordance with these embodiments, the powder formulation includes a benzodiazepine, preferably clobazam or clonazepam, and an additive material. The powder includes at least 60% by weight of the

benzodiazepine based on the weight of the powder. Advantageously, the powder comprises at least 70%, more preferably at least 80% by weight of benzodiazepine based on the weight of the powder. Most advantageously, the powder comprises at least 90%, and more preferably at least 95%, of benzodiazepine based on the weight of the powder.

It is believed that there are physiological benefits associated with introducing as little powder as possible to the lungs, in particular material other than the active agent to be administered to the patient to produce the desired therapeutic effect. Therefore, the amounts of additive material included in the dry powder composition is preferably as small as possible. The most preferred powder composition would, therefore, comprise more than 99% by weight of benzodiazepine.

In these "carrier free" formulations, at least 90% by weight of the particles if the powder have a particle size of less than 20μm, preferably less than 10μm and more preferably less than 5μm. As indicated above, the size of the benzodiazepine particles of the powder should be within the range of from 0.1μm to 5μm for effective delivery to the lower lung. Where the additive material is in the form of particles of material, it may be advantageous for particles of the additive material to have a size range above the preferred range for delivery to the lower lung.

It is considered to be particularly advantageous for the additive material to comprise an amino acid. When present as an additive material in a dry powder composition, amino acids have been found to give a high respirable fraction of the active material and also enhance the flow properties of the powder. A preferred amino acid is leucine, in particular L-leucine. Although the L-form of the amino acids is disclosed herein as being preferred, the D- and DL-forms may also be used. The additive material may comprise one or more of the following amino acids: leucine, isoleucine, lysine, valine, methionine, cysteine and phenylalanine. Preferably, the powder comprises at least 80% and preferably at least 90% by weight of benzodiazepine (or its pharmaceutically acceptable salts) based on the weight of the powder. Preferably, the powder includes not more than 8%, more preferably not more than 5% by weight of additive material based on the weight of the powder. As

indicated above, in some cases it will be advantageous for the powder to contain about 1% by weight of additive material. The additive material may also be magnesium stearate or colloidal silicon dioxide.

In an attempt to assist deagglomeration of the particles within the composition and to provide a consistent FPF and FPD, dry powder formulations often include coarse carrier particles of excipient material mixed with fine particles of active material. Rather that sticking to one another, the fine active particles tend to adhere to the surfaces of the coarse carrier particles whilst in the inhaler device, but are supposed to release and become dispersed upon actuation of the dispensing device and inhalation into the respiratory tract, to give a fine suspension. The carrier particles preferably have MMADs greater than 40μm.

The inclusion of coarse carrier particles is also very attractive where very small doses of active agent are dispensed. It is very difficult to accurately and reproducibly dispense very small quantities of powder and small variations in the amount of powder dispensed will mean large variations in the dose of active agent where the powder comprises mainly active particles. Therefore, the addition of a diluent, in the form of large excipient particles will make dosing more reproducible and accurate.

Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles are of a polyol. In particular, the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Therefore, in a further preferred embodiment, the compositions of the present invention also comprise carrier particles.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 10μm and 1000μm, more preferably between 50μm and 1000μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355μm and lies between 20μm and 250μm.

Preferably at least 90% by weight of the carrier particles have a diameter between from 60μm to 1000μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratios in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 95% based on the combined weight of the composite active particles and the carrier particles.

A further difficulty is encountered when adding coarse carrier particles to a composition of fine active particles and that difficulty is ensuring that the fine particles detach from the surface of the large particles upon actuation of the delivery device.

The step of dispersing the active particles from other active particles and from carrier particles, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials, including FCAs of the nature discussed above. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649 and WO 96/23485.

In some embodiments of the present invention, the powder composition may further comprise fine particles of an excipient material, which may, for example, be a material such as one of those mentioned herein as being suitable for use as a carrier material. Especially useful in this respect are materials such as crystalline sugars such as dextrose or lactose. Where both types of particles are present, the fine excipient particles may be of the same material as the carrier particles, or of a different material.

The particle size of the fine excipient material will generally not exceed 30μm, and preferably does not exceed 20μm. In some circumstances, for example where any carrier particles and/or any fine excipient particles are of a material which is itself capable of inducing a sensation in the oropharangeal region, the carrier particles and/or fine excipient particles can constitute an indicator material. For example, the carrier particles and/or any fine particle excipient may comprise mannitol.

In some embodiments of the present invention, the powder for inhalation may be prepared by mixing the components of the powder together. For example, the powder may be prepared by mixing together particles of active material and the carrier material and/or additive material. The type of equipment used will depend on the particular formulation used. For example, for certain formulations a relatively low shear mixer such as the Inversina Variable Tumbler Mixer may be used. For other formulations, a higher shear mixer such as Retch Grindomix mixer is more appropriate. For yet other formulations, a mechanofusion system such as the Hosokawa Mechano-Fusion mill may be used. In some cases, spheronisation may be advantageous.

It is preferred for the dry powder compositions of the present invention to be such that a fine particle fraction of at least 35% is produced upon actuation of the inhaler device. It is more preferred that the fine particle fraction be greater than or equal to 50%. It is particularly preferred that the fine particle fraction be greater than or equal to 60%. It is especially preferred that the fine particle fraction be greater than or equal to 70%. It is most preferred that the fine particle fraction be greater than or equal to 80%. The term fine particle fraction is used here to denote the fraction

of the total amount of active material delivered by the device which has a diameter of not more than 5μm. The total amount of active material delivered by the device is in general less than the amount of active material that is metered in the device or is present in a pre-metered dose within the device.

Thus, in certain embodiments of the present invention, a benzodiazepine dry powder composition is provided for use in an inhaler device. Such compositions preferably further comprise a carrier material. The powder will preferably generate a fine particle fraction of at least 35%, preferably at least 50%, more preferably at least 60% and most preferably at least 70%, upon actuation of the inhaler device.

Upon actuation of the dispensing device, the powder formulation becomes entrained in an airflow which is generated (actively or passively) within the device. The manner in which the powder becomes entrained in this airflow and is then expelled from the device is also crucial in ensuring that as much of the active agent is dispensed as possible.

It is not simply a question of entraining as much of the powder as possible in the airflow. In addition, the entrainment should be such that the plume of powder expelled from the device is such that deposition of the active agent in the throat is minimised. Finally, it is also desirable for any agglomerates in the powder to be broken up as the powder becomes entrained in the airflow.

This deagglomeration is possible where the airflow is controlled so that it applies shear forces on the powder formulation as it becomes entrained in the airflow. These shear forces can serve to break up agglomerated particles, thereby enhancing the FPF and FPD of the powder.

One way in which deagglomeration of agglomerates in the dry powder formulation may be achieved during powder entrainment within the dispensing device it to arrange the airflow so that it applies shear forces to the powder, breaking the agglomerates apart.

In addition to deagglomeration, it is also very important for the entrainment of the powder in the airflow to be as efficient as possible, leaving as little powder behind as possible. Finally, another consideration is the dynamics of the powder as it leaves the inhaler device. Once again, this is linked to the entrainment of the powder in the airflow.

Naturally, the entrainment of the dry powder formulation in an airflow will be affected by the properties of the formulation itself, as well as the device used. For example, entrainment of a fine powder, that is, one which does not include a population of larger particles, such as carrier particles, is more difficult than entrainment of a powder comprising a combination of large and fine particles. However, the arrangement of the device itself also affects the powder entrainment. In particular, it is the path of the airflow through the powder and out of the device which will determine any deagglomeration, powder entrainment and powder velocity, etc.

According to an aspect of the present invention, a method is provided comprising entraining agglomerated particles in a gas flow. The method comprises depositing the agglomerate particles onto one or more surfaces, and applying, via the gas flow, a shear to the deposited agglomerated particles to deagglomerate them.

A "high turbulence inhaler device" is to be understood as meaning an inhaler device which is configured to generate relatively high turbulence within the device and/or a relatively high incidence of impaction of powder upon internal surfaces and/or obstructions within the device, whereby efficient de-agglomeration of agglomerated powder particles occurs in use of the device.

The dry powder inhaler devices in which the powder composition of the present invention will be commonly used include "single dose" devices, for example the Rotahaler™, the Spinhaler™ and the Diskhaler™ in which individual doses of the powder composition are introduced into the device in, for example, a capsule or a blister. "Multiple dose" devices may also be used, such as the Turbohaler™ in

which, on actuation of the inhaler, one dose of the powder is removed from a reservoir of the powder material contained in the device.

As previously mentioned, in the case of certain powder compositions, a form of device that promotes high turbulence offers advantages in that a higher fine particle fraction will be obtainable than in the use of other forms of device. Such devices include, for example, the Turbohaler™ or Novolizer™, and may be devices of the kind in which generation of an aerosolised cloud of powder is driven by inhalation of the patient or of the kind having a dispersal device for generating or assisting in the generation of the aerosolised cloud of powder for inhalation.

In one embodiment, the method comprises entraining a powdered substance in a gas flow stream from an inlet port of a vortex chamber having a substantially circular cross-section. The method further comprises directing the gas flow through the vortex chamber in a tangential direction; directing the gas flow through the vortex chamber so as to aerosolise the powder composition; and directing the gas flow with the powder composition out of the vortex chamber in an axial direction through an exit port. Preferably, the velocity of the gas flow at a distance of 300mm outside of the exit port is less than the velocity of the gas flow at the inlet port.

In another embodiment, the method comprises entraining a powdered composition including agglomerated particles in a gas flow upstream from an inlet port of the vortex chamber. In this embodiment, the method comprises directing the gas flow through the inlet port into the vortex chamber; depositing the agglomerated particles onto one or more of the walls of the vortex chamber; applying, via the gas flow through the vortex chamber, a shear to the deposited agglomerated particles to deagglomerate the particles; and directing the gas flow, including the deagglomerated particles, out of the vortex chamber; wherein the velocity of the gas flow at a distance of 300mm outside the exit port is less than the velocity of the gas flow at the inlet port.

The invention further provides an arrangement for generating an air flow through a chamber containing powder, so that the powder becomes entrained in the air flow and is carried out of the chamber via an exit port. This involves directing the

airflow through the chamber. The chamber has an axis and a wall curved around the axis and the air rotates around this axis. The airflow is also directed through an inlet port of the chamber, wherein the direction of the airflow through the inlet port is tangential to the chamber wall. The direction of the airflow through the exit port is parallel to the axis. A cross-sectional area of the airflow through the chamber is in a normal plane to the airflow and decreases with increasing distance from the inlet port.

In another aspect, an inhaler is provided, for providing the airflow and deagglomeration discussed above. Such inhalers comprise an aerosolising device including a substantially tangential inlet port and a substantially axial exit port. The inhalers also comprise one or more sealed blisters (or capsules) containing the pharmaceutical dry powder composition to be dispensed, and an input device for removably receiving one of these blisters. Upon actuation, the inhaler couples the tangential inlet port with the powder composition in the received blister.

With regard to the aerosolising device, in some embodiments, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and a substantially axial outlet port. Preferably, the ratio of the diameter of the vortex chamber to the diameter of the exit port is between 4 and 12.

In other embodiments, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port, wherein the inlet port has an outer wall which defines the maximum extent of the inlet port in the radially outward direction of the vortex chamber. The extent of the outer wall in the axial direction of the vortex chamber is substantially equal to the maximum extent of the inlet port in the axial direction of the vortex chamber, the outer wall is substantially parallel with a wall of the vortex chamber.

In other embodiments, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port. A bottom surface defines the furthest extent of the vortex chamber from the exit port

in the axial direction, and the bottom surface further defines the furthest axial extent of the inlet port from the exit port.

In yet further embodiments, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use, wherein the cross-sectional area of the inlet conduit decreases towards the vortex chamber. The inlet conduit is, upon actuation of the inhaler, coupled to the powder composition in the received blister.

In other embodiments, the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and an arcuate inlet conduit arranged to supply a powdered composition entrained in a gas flow to the inlet port, in use. The inlet conduit is, upon actuation of the inhaler, coupled to the powder composition in the received blister.

In other embodiments, the aerosolising device is in the form of a vortex chamber having an axis defined, at least in part, by a wall which forms a curve about the axis. The vortex chamber has a cross-sectional area in a plane bounded by the axis, and the plane extends in one direction radially from the axis at a given angular position (θ) about the axis. The vortex chamber has a substantially tangential inlet port and a substantially axial exit port, and said cross-sectional area of the vortex chamber decreases with increasing angular position (θ) in the direction, in use, of the gas flow between the inlet port and the outlet port.

In other embodiments, the aerosolising device is in the form of a vortex chamber having an axis defined, at least in part, by a wall which forms a curve about the axis. The vortex chamber has a substantially tangential inlet port and a substantially axial exit port. The vortex chamber is further defined by a base, and the distance (d) between the base and a plane which is normal to the axis and is located on the opposite side of the base to the exit port increase with radial position (r) relative to the axis.

In other embodiments, the aerosolising device includes as chamber defined by a top wall, a bottom wall, and a lateral wall, the lateral wall being curved about an axis which intersects the top wall and the bottom wall. The chamber encloses a cross-sectional area defined by the axis, the top wall, the bottom wall and the lateral wall, and the chamber has an inlet port and an outlet port. The inlet port is tangential to the lateral wall, the outlet port is co-axial with the axis, and the cross-sectional area decreases with increasing angular position from the inlet port in a direction of a gas flow through the inlet port.

In still other embodiments, the aerosolising device is a chamber including a wall, a base, an inlet port and an exit port. The chamber has an axis that is co-axial with the exit port and intersects the base. The wall is curved about the base, the inlet port is tangential to the wall, and a height between the base and a plane normal to the axis at the exit port decreases as a radial position from the axis to the inlet port increases.

In certain aspects of the invention, particularly wherein the composition has been prepared using a process involving mechanofusion and/or jet-milling, pharmaceutical compositions in accordance with the invention comprise a benzodiazapine for administration by inhalation, but do not consist or consist essentially of clobazam (i.e., of the drug alone or in substantial isolation), consist of or comprise clobazam and leucine, and/or consist of or comprise clobazam and magnesium stearate. The clobazam may be in the form of a pharmaceutically acceptable salt.

In further aspects of the invention, pharmaceutical compositions in accordance with the invention can consist or consist essentially of clobazam, consist of or comprise clobazam and leucine, or consist of or comprise clobazam and magnesium stearate. Pharmaceutical compositions in accordance with this last aspect are preferably formed by mechanofusion and/or jet-milling. The clobazam may be in the form of a pharmaceutically acceptable salt.

In yet further aspects of the invention, wherein the composition has been prepared using a process involving spray-drying, spray-drying using a spray-dryer comprising a means for producing droplets moving at a controlled velocity, or co-spray drying with a force control agent, pharmaceutical compositions in accordance with the invention comprise a benzodiazapine for administration by inhalation, but do not comprise clobazam. In an alternative aspect, wherein the pharmaceutical composition comprises clobazam, it is prepared by spray-drying, spray-drying using a spray dryer comprising means for producing droplets moving at a controlled velocity, or co-spray drying with a force control agent. The clobazam may be in the form of a pharmaceutically acceptable salt.

One embodiment of the invention is described in detail, by way of example only, with reference to the following drawings.

Figure 1 shows an inhaler and blister in accordance with an embodiment of the present invention.

Figure 2 is a top cross-section of a vortex nozzle 1.

Figure 3 is a side cross-section of a vortex chamber in accordance with an embodiment of the invention.

Figure 4 is a sectional view along line B-B of the vortex chamber of Figure 3.

Figure 5(a) is a side view of a vortex chamber with a round inlet port.

Figure 5(b) is a sectional view along line D-D of the vortex chamber of Figure 5(a).

Figure 6(a) is a side view of a vortex chamber with a rectangular inlet port.

Figure 6(b) is a sectional view along line E-E of the vortex chamber of Figure 6(a).

Figure 7 shows a vortex chamber with an arcuate inlet conduit.

Figures 8 to 11 show detail of embodiments of the exit port of the inhaler in accordance with the invention.

Figure 12 illustrates an asymmetric vortex chamber in accordance with an embodiment of the invention.

Figure 13 is a sectional view of a vortex chamber in accordance with another asymmetric inhaler in accordance with an embodiment of the invention.

Figure 14 is a perspective view of a vortex chamber according to Figure 13.

Figure 15 is a sectional view of the vortex chamber of Figure 14.

Figure 16 is a perspective view of a detail of the vortex chamber of Figures 14 and 15;

Figure 17 is a plan view of the detail of Figure 16.

Figure 18 is a plan view of a variation of the detail of Figure 17.

Figures 19 to 21 show variations of the interface between the wall and the base of a vortex chamber according to the embodiments of Figures 13-18.

Figures 22(A) and 22(B) illustrate the particle size distribution of the lactose of Example 1.

Figure 23 shows a perspective view of the prototype inhaler used to perform inhalation testing.

Figure 24 shows the inhaler of Figure 23 with its cover removed to show the breath actuation mechanism and vortex nozzle.

Figure 25 is a cross-section view through the vortex nozzle taken along line AA in Figure 24.

Figure 26a is a cross-section view taken along line BB in Figure 24 showing the nozzle valve in the closed position.

Figure 26b is a cross-section view taken along line BB in Figure 24 showing the nozzle valve in the open position.

Figures 27a is a cross-section view taken along line BB in Figure 24 showing the nozzle valve in the closed position.

Figure 27b is a cross-section view taken along line BB in Figure 24 showing the nozzle valve in the open position.

Figure 28 shows the results of a particle size analysis of a preferred micronised leucine.

Figures 1a and 1b show schematically alternative embodiments of an inhaler that can be used to deliver the powder formulations described above to a patient. Figure 1a shows a breath-actuated embodiment while Figure 1b shows a manually actuated embodiment. Inhalers of this type are described in WO 02/089880 and WO 02/089881, both published on 14 November 2002, the entire disclosures of which are hereby incorporated by reference. Figures 2-7 correspond to the inhalers described in WO 02/089880, Figures 12-21 correspond to the inhalers described in WO 02/089881, and Figures 8-11 show preferred exit port configurations that can be used in connection with any of these inhalers.

Referring to Figures 1a, 1b and 2, the inhaler comprises a nozzle 3000 including a vortex chamber 1 and having an exit port 2 and an inlet port 3 for generating an aerosol of the powder formulation. The vortex chamber 1 is located in a mouthpiece 10 through which the user inhales to use the inhaler. Air passages (not

shown) may be defined between the vortex chamber 1 and the mouthpiece 10 so that the user is able to inhale air in addition to the powdered medicament.

The powder formulation is stored in a blister 60 defined by a support 70 and a pierceable foil lid 75. As shown, the support 70 has a cavity formed therein for holding the powder formulation. The open end of the cavity is sealed by the lid 75. An air inlet conduit 7 of the vortex chamber 1 terminates in a piercing head (or rod) 50 which pierces the pierceable foil lid 75. A reservoir 80 is connected to the blister 60 via a passage 78. A regulated air supply 90 charges the reservoir 80 with a gas (e.g., air, in this example) to a predetermined pressure (e.g. 1.5 bar). Preferably, the blister contains from 1 to 5 mg of powder formulation, preferably 1, 2 or 3 mg of powder formulation.

In certain embodiments, the support 70 is also made of foil. Such blisters are commonly referred to in the art as double-foil blisters. In other embodiments of the present invention, the support 70 is made of a polymer. It is believed that the foil support 70 provides greater protection against moisture and oxidation than the polymer support 70.

Referring to Figure 1a, when the user inhales, a valve 40 is opened by a breath-actuated mechanism 30, forcing air from the pressurised air reservoir through the blister 60 where the powdered formulation is entrained in the air flow. The manually actuated inhaler of Figure 1b requires the depression of a button 12 to open the valve 40 and create the aforementioned air flow. Either embodiment may be used with a face mask 45 that attaches to the mouthpiece 10.

Where a caretaker is administering the formulation, the manually-actuated embodiment of Figure 1b is used. The face mask 45 is placed over the nose and mouth of a patient (not shown) and the actuation button 12 depressed to open the valve 40 and create the necessary airflow to carry the formulation particles to the lung, the process of which is discussed below.

In both embodiments, the air flow transports the powder formulation to the vortex chamber 1, where a rotating vortex of powder formulation and air is created between the inlet port 3 and the outlet port 2. Rather than passing through the vortex chamber in a continuous manner, the powdered formulation entrained in the airflow enters the vortex chamber in a very short time (typically less than 0.3 seconds and preferably less than 20 milliseconds) and, in the case of a pure drug formulation (i.e., no carrier), a portion of the powder formulation sticks to the walls of the vortex chamber. This powder is subsequently aerosolised by the high shear forces present in the boundary layer adjacent to the powder. The action of the vortex deagglomerates the particles of powder formulation, or in the case of a formulation comprising a drug and a carrier, strips the drug from the carrier, so that an aerosol of powdered formulation exits the vortex chamber 1 via the exit port 2. The aerosol is inhaled by the user through the mouthpiece 10.

The vortex chamber 1 can be considered to perform two functions: deagglomeration, the breaking up of clusters of particles into individual, respirable particles; and filtration, preferentially allowing particles below a certain size to escape more easily from the exit port 2. Deagglomeration breaks up cohesive clusters of powdered formulation into respirable particles, and filtration increases the residence time of the clusters in the vortex chamber 1 to allow more time for them to be deagglomerated. Deagglomeration can be achieved by creating high shear forces due to velocity gradients in the airflow in the vortex chamber 1. The velocity gradients are highest in the boundary layer close to the walls of the vortex chamber.

As shown in more detail in Figure 2, the vortex chamber 1 of Figures 2 to 7 is in the form of a substantially cylindrical chamber. The vortex chamber 1 has a frustoconical portion in the region of the exit port 2. The inlet port 3 is substantially tangential to the perimeter of the vortex chamber 1 and the exit port 2 is generally concentric with the axis of the vortex chamber 1. Thus, gas enters the vortex chamber 1 tangentially via the inlet port 3 and exits axially via the exit port 2. Between the inlet port 3 and the exit port 2 a vortex is created in which shear forces are generated to deagglomerate the particles of medicament. The length of the exit

port 2 is preferably minimized to reduce the possibility of deposition of the drug on the walls of the exit port 2. In the embodiment shown, the vortex chamber 1 is machined from polyetheretherketone (PEEK), acrylic, or brass, although a wide range of alternative materials is possible.

The ratio of the diameter of the vortex chamber to the diameter of the exit port can be significant in maximising the fine particle fraction of the medicament aerosol which is expelled from the exit port. Thus, the ratio of the diameter of the vortex chamber to the diameter of the exit port may be between 4 and 12. It has been found that when the ratio is between 4 and 12 the proportion of particles of the powdered medicament with an effective diameter in the range 1 to 3 microns is maximised. For an enhanced fine particle fraction, the ratio is preferably greater than 5, most preferably greater than 6 and preferably less than 9, most preferably less than 8. In the preferred arrangement, the ratio is 7.1.

In certain embodiments of the invention, the diameter of the vortex chamber is between 2 and 12 mm. The diameter of the vortex chamber is preferably greater than 4 mm, most preferably at least 5 mm and preferably less than 8 mm, most preferably less than 6 mm. In the preferred embodiment, the diameter of the vortex chamber is 5 mm. In these embodiments, the height of the vortex chamber is generally between 1 and 8 mm. The height of the vortex chamber is preferably less than 4 mm, most preferably less than 2 mm. In the preferred embodiment, the height of the vortex chamber is 1.6 mm. In general, the vortex chamber is substantially cylindrical. However, the vortex chamber may take other forms. For example, the vortex chamber may be frustoconical. Where the diameter of the vortex chamber or the exit port is not constant along its length, the ratio of the largest diameter of the vortex chamber to the smallest diameter of the exit port should be within the range specified above. The aerosolising device comprises an exit port, for example as described above. The diameter of the exit port is generally between 0.5 and 2.5 mm. The diameter of the exit port is preferably greater than 0.6 mm and preferably less than 1.2 mm, most preferably less than 1.0 mm. In the preferred embodiment, the diameter of the exit port is 0.7 mm.

Table 1 - Symmetrical Vortex chamber dimensions

Dimension		Preferred Value
D	Diameter of chamber	5.0mm
H	Height of chamber	1.6mm
h	Height of conical part of chamber	0.0mm
D_e	Diameter of exit port	0.7mm
t	Length of exit port	0.3mm
a	Height of inlet port	1.1mm
b	Width of inlet port	0.5mm
α	Taper angle of inlet conduit	12°

Figures 3 and 4 show the general form of the vortex chamber of the inhaler of Figure 1. The geometry of the vortex chamber is defined by the dimensions listed in Table 1. The preferred values of these dimension are also listed in Table 1. It should be noted that the preferred value of the height h of the conical part of the chamber is 0 mm, because it has been found that the vortex chamber functions most effectively when the top of the chamber is flat.

As shown in Table 2, the proportion of the particles of medicament emitted in the aerosol having an effective particle diameter of less than 6.8 microns generated by the vortex chamber (the 6.8 micron particle fraction) depends on the ratio of the diameters of the chamber D and the exit port D_e. The normalised average 6.8 micron particle fraction is the emitted 6.8 micron particle fraction divided by the 6.8 micron particle fraction of the powdered medicament loaded into the inhaler. The medicament used was pure Intal™ sodium cromoglycate (Fisons UK).

Table 2- Relationship between emitted 6.8 micron particle fraction and ratio of vortex chamber diameter to exit port diameter.

Ratio D/D_e	Average particle fraction <6.8μm (%)	Normalised average particle fraction <6.8μm (%)
2.0	64.7	73.1
3.1	70.8	79.9

4.0	75.5	85.2
6.0	81.0	91.4
7.1	83.5	94.3
8.0	83.2	93.9
8.6	80.6	91.0

It will be seen from the above table that where the ratio of the diameters of the chamber and the exit port is 4 or more, the normalised 6.8 micron particle fraction is over 85%. Thus, the deagglomeration efficiency of the vortex chamber is significantly improved where the ratio is in this range. With the preferred ratio of 7.1, a normalised 6.8 micron particle fraction of 94.3% has been achieved.

Figures 5a and 5b show a vortex chamber 1 in which the inlet port 3 has a circular cross-section. As represented by the solid arrow in Figure 5b, a portion of the airflow entering the vortex chamber via the inlet port 3 follows the lateral wall 12 of the vortex chamber 1. The powder entrained in this airflow is therefore introduced directly into the airflow at the boundary layer adjacent the lateral wall 12 of the vortex chamber 1, where the velocity gradient in the radial direction is at a maximum. The maximal velocity gradient results in maximal shear forces on the agglomerated particles of the powder and thus maximum deagglomeration.

However, as represented by the dashed arrow in Figure 5b, a portion of the airflow entering the vortex chamber via the inlet port 3 does not follow the chamber wall 12, but rather crosses the chamber 1 and meets the wall 12 at a point opposite the inlet port 3. At this point, there is increased turbulence, because the flow must make an abrupt change of direction. This turbulence disturbs the boundary layer adjacent the wall 12 of the chamber 1 and thereby reduces the effectiveness of the deagglomeration of the powder.

Figures 6a and 6b show a vortex chamber 1 in which the inlet port 3 has a rectangular cross-section. The rectangular cross-section maximises the length of the perimeter of the inlet port that is coincident with the wall 12 of the vortex chamber 1, such that the maximum air flow is introduced into the boundary layer of the

vortex. Similarly, the rectangular cross-section maximises the width of the perimeter of the inlet port 3 that is coincident with the bottom surface 13 of the vortex chamber 1. In this way, deposition of powder in the vortex chamber 1 is prevented, because the vortex occupies the entire chamber 1.

In addition to having a rectangular cross-section, the inlet port 3 of Figures 6a and 6b is supplied by an inlet conduit 7 which tapers towards the vortex chamber 1. Thus, the inlet conduit 7 is defined by an inner wall 14 and an outer wall 15. The outer wall 15 is substantially tangential to the wall 12 of the vortex chamber 1. The spacing of the inner wall 14 from the outer wall 15 decreases towards the vortex chamber 1, so that the inner wall 14 urges the air flow into the vortex chamber 1 towards the boundary layer.

Furthermore, the decreasing cross-sectional area of the inlet conduit 7 causes the flow of velocity to increase, thereby reducing deposition of powder on the way to the vortex chamber 1.

As indicated by the arrows in Figure 6b, all of the airflow entering the vortex chamber via the inlet port 3 follows the wall 12 of the vortex chamber 1. The powder entrained in this airflow is therefore introduced directly into the airflow at the boundary layer adjacent the wall 12 of the vortex chamber 1, and deagglomeration is maximised.

A further improvement can also be achieved if the upper surface 16 of the vortex chamber 1 is flat, as shown in Figures 8 to 10, rather than conical as shown in Figures 1, 3, 5 and 6. Thus, in this arrangement, the upper surface 16 of the vortex chamber 1 is substantially perpendicular to the wall 12 of the chamber 1, and to the axis of the vortex.

Figures 8 to 11 show various options for the exit port 2 of the vortex chamber 1. The characteristics of the exit plume of the aerosol are determined, at least in part, by the configuration of the exit port 2. For example, if the aerosol leaves an exit port 2 of 1 mm diameter at a flow rate of 2 litres/minute, the velocity at the exit

port 2 will be approximately 40 m/s. This velocity can be reduced to a typical inhalation velocity of 2 m/s within a few centimetres of the chamber or nozzle by providing a strongly divergent aerosol plume.

In Figure 8, the exit port 2 is a simple orifice defined through the upper wall 17 of the vortex chamber 1. However, the thickness of the upper wall 17 means that the exit port 2 has a length which is greater than its diameter. Thus, there is a risk of deposition in the exit port as the aerosol of powder exits. Furthermore, the tubular exit port tends to reduce the divergence of the exit plume. These problems are solved in the arrangement of Figure 9 by tapering the upper wall 17 of the vortex chamber 1 towards the exit port 2 so that the exit port 2 is defined by a knife edge of negligible thickness. For an exit port 2 of diameter 1 mm, an exit port length of 2.3 mm gives a plume angle of 60E, whereas reducing this length to 0.3 mm increases the angle to 90E.

In Figure 10, the exit port 11 is annular and is also defined by a knife edge. This arrangement produces an exit plume that slows down more quickly than a circular jet, because the annular exit port has a greater perimeter than a circular port of the same diameter and produces a jet that mixes more effectively with the surrounding static air. In Figure 11, multiple orifices form the exit port 2 and produce a number of smaller plumes which break up and slow down in a shorter distance than a single large plume.

Figure 7 shows an embodiment of the vortex chamber 1 in which the inlet conduit 7 is arcuate and tapers towards the vortex chamber 1. As shown by the arrows in Figure 13, the arcuate inlet conduit 7 urges the entrained particles of powdered formulation towards the outer wall 15 of the inlet conduit 7. In this way, when the powder enters the vortex chamber 1 through the inlet port 3 the powder is introduced directly into the boundary layer next to the wall 12 of the vortex chamber 1, where shear forces are at a maximum. In this way, improved deagglomeration is achieved.

The inhaler in accordance with embodiments of the invention is able to generate a relatively slow moving aerosol with a high fine particle fraction. The inhaler is capable of providing complete and repeatable aerosolisation of a measured dose of powdered drug and of delivering the aerosolised dose into the patient's inspiratory flow at a velocity less than or equal to the velocity of the inspiratory flow, thereby reducing deposition by impaction in the patient's mouth. Furthermore, the efficient aerosolising system allows for a simple, small and low cost device, because the energy used to create the aerosol is small. The fluid energy required to create the aerosol can be defined as the integral over time of the pressure multiplied by the flow rate. This is typically less than 5 joules and can be as low as 3 joules.

Figures 12-21 show asymmetric inhalers in accordance with other embodiments of the present invention with similar components bearing identical reference numbers to the embodiments described above.

Initially, it should be noted that the difference between these embodiments and the embodiments described above with regard to Figures 1-11 is that, in the embodiments shown in Figures 12-21, the vortex chamber 1 has an asymmetric shape.

In the embodiment shown in Figure 12, the wall 12 of the vortex chamber 1 is in the form of a spiral or scroll. The inlet port 3 is substantially tangential to the perimeter of the vortex chamber 1 and the exit port 2 is generally concentric with the axis of the vortex chamber 1. Thus, gas enters the vortex chamber 1 tangentially via the inlet port 3 and exits axially via the exit port 2. The radius R of the vortex chamber 1 measured from the centre of the exit port 2 decreases smoothly from a maximum radius R_{max} at the inlet port 3 to a minimum radius R_{min}. Thus, the radius R at an angle 2 from the position of the inlet port 3 is given by $R=R_{max}(1-2k/2B)$, where $k=(R_{max}-R_{min})/R_{max}$. The effective radius of the vortex chamber 1 decreases as the air flow and entrained particles of medicament circulate around the chamber 1. In this way, the effective cross-sectional area of the vortex chamber 1 experienced by the air flow decreases, so that the air flow is accelerated and there is reduced deposition of the entrained particles of medicament. In

addition, when the flow of air has gone through 2B radians (360E), the air flow is parallel to the incoming airflow through the inlet port 3, so that there is a reduction in the turbulence caused by the colliding flows.

Between the inlet port 3 and the exit port 2 a vortex is created in which shear forces are generated to deagglomerate the particles of the powdered formulation. As discussed above, the length of the exit port 2 is preferably as short as possible to reduce the possibility of deposition of the drug on the walls of the exit port 2. In the embodiment shown, the vortex chamber 1 is machined from PEEK, acrylic, or brass, although a wide range of alternative materials is possible. For manufacturing ease, the radius of the vortex chamber 1 may decrease in steps rather than smoothly.

Figure 13 shows the general form of the vortex chamber of the inhaler of Figure 12. The geometry of the vortex chamber is defined by the dimensions listed in Table 3. The preferred values of these dimension are also listed in Table 3. It should be noted that the preferred value of the height h of the conical part of the chamber is 0 mm, because it has been found that the vortex chamber functions most effectively when the top (roof 16) of the chamber is flat.

Table 3 - Asymmetrical Vortex chamber dimensions

Dimension		Preferred Value
R_{max}	Maximum radius of chamber	2.8mm
R_{min}	Minimum radius of chamber	2.0mm
H_{max}	Maximum height of chamber	1.6mm
h	Height of conical part of chamber	0.0mm
D_e	Diameter of exit port	0.7mm
t	Length of exit port	0.3mm
a	Height of inlet port	1.1mm
b	Width of inlet port	0.5mm
α	Taper angle of inlet conduit	9°, then 2°

The 6.8 micron particle fraction of the aerosol generated by the vortex chamber 1 according to Figure 12 is improved relative to a circular vortex chamber of Figures 1-11.

Figures 14 to 18 show another asymmetric inhaler in accordance with the present invention in which the vortex chamber 1 includes a ramp 20 which reduces the height of the vortex chamber 1 from the bottom up with increasing angular displacement 2 from the inlet port 3. A substantially circular region 21 in the centre of the vortex chamber 1 remains flat.

Various options for the cross-section of the ramp 20 are shown in Figures 19 to 21. As shown in Figure 19, the cross-section of the ramp 20 may be a curve, such as a conic section. The value of the radius (or radii) of the curve may increase with increasing angular displacement 2 about the axis of the vortex chamber 1.

Preferably, as shown in Figure 20, the ramp 20 has a triangular cross-section, with an angle $ between the base and the upper surface of the ramp 20. The angle $ is a function of the angular displacement 2, such that $\$=q(2-2_1)$ where 2_1 and q are constants.

As shown in Figure 21, the joints between the ramp 20 and the wall 12 of the vortex chamber and the ramp 20 and the base of the vortex chamber 1 are curved, for example with a fillet radius, to prevent unwanted deposition in this region.

The vertical face (normal to the base) of the ramp 20 where the ramp meets the inlet 3 is likely to attract deposition because of the abrupt change in height. However, by arranging the profile of the face (looking axially) to form a smooth entry, as shown in Figure 17, contiguous with the inner edge of the inlet 3 air travelling from the inlet scours the face and prevents powder build up.

In one arrangement the profile is a straight line at 40° (angle N in Figure 18) to the centre line of the inlet, joined to the inlet wall by a tangent curve. This profile

follows the pattern of deposition that would be seen in a similar nozzle without a ramp.

In a preferred embodiment the profile is a curve moving radially inward as shown in Figure 17. At one end it joins the inner wall of the inlet tangentially. At the other end it joins a continuation of the inner curve of the ramp at the point where the ramp meets the base.

Examples

Example 1: Preparation of Lactose

A sieved fraction of Respitose SV003 (DMV International Pharma, The Netherlands) lactose is manufactured by passing bulk material through a 63μm sieve. This material is then sieved through a 45μm screen and the retained material is collected. Figures 22(A) and 22(B) show the results of a particle size analysis of two batches of the lactose performed with a Mastersizer 2000, manufactured by Malvern Instruments, Ltd. (Malvern, UK). As shown, the lactose had a volume weighted mean of from about 50 to about 55 microns, a d_{10} of from about 4 to about 10 microns, a d_{50} of from about 50 to about 55 microns, and a d_{90} of from about 85 to about 95 microns wherein d_{10} d_{50} d_{90} refer to the diameter of 10%, 50%, and 90% of the analyzed lactose.

Example 2: Preparation of 1 Milligram Benzodiazepine-Lactose Formulation

The benzodiazepine clobazam is micronised such that 90% of the particles had a diameter of less than 5μm.

50 grams if the lactose of Example 1 was placed into a metal mixing vessel of a suitable mixer. 50 grams of the micronised benzodiazepine are then added. An additional 50 grams of the lactose of Example 1 is then added to the mixing vessel, and the resultant mixture is tumbled for 15 minutes. The resultant blend is then passed through a 150μm screen. The screened blend (i.e. the portion of the blend that passed through the screen) is then reblended for 15 minutes.

In certain batches, the mixer used is an Inversina Variable Speed Tumbler Mixer, which is a low shear mixer distributed by Christison Scientific Equipment Ltd of Gateshead, UK. In other batches, the mixer used was a Retch Grindomix mixer is a higher shear mixer which is also distributed by Christison Scientific Equipment Ltd. Disaggregation was shown to be sensitive to the intensity of the mixing process but a consistent fine particle fraction (about 60%) was obtained using a low shear mixer equipped with a metal vessel such as the Inversina mixer referenced above.

Example 3: Incorporation of Formulation into Blisters

The formulation of Example 2 is incorporated into blisters in the following manner. Three milligrams of the benzodiazepine-lactose formulation were placed in each blister. As described above in connection with Figure 1, the base of each blister is a cold-formed aluminum blister, formed from a laminate of oriented polyamide (exterior), 45 microns of aluminum (center), and PVC (interior). The lid of the blister is made of a hard-rolled 30 micron lidding foil, having a heat seal lacquer. After the formulation is loaded into the interior of the blisters, the blisters are sealed by placing the lid over the blister base, and heat sealing the lid to the base via the heat seal lacquer.

Although the above referenced examples utilize a blister "fill weight" of 3mg, it should be appreciated that larger or smaller fill weights may also be used. For example, in Examples 4 and 5 below, fill weights of 4 and 5mg are provided. Although a variety of techniques for filling blisters to such fill weights may be used it is believed that commercial production of blisters with 1mg and 2mg fill weights can be achieved with a Harro-Hoefliger Omnidose Drum Filler. Lower fill weights, and in particular fill weights of the order of 1mg, are believed to provide superior fine particle fractions as compared to higher fill weights.

The above-referenced blisters containing the 1mg benzodiazepine-lactose formulations can be tested using the prototype inhaler shown in Figures 23 to 29. Referring to Figures 23 and 24, the inhaler comprises a reservoir 80 (not shown) which provides a charge of compressed air, a base block 2000, an airway 2004, a mouthpiece 10 through which the dose is inhaled, a blister loader 2010 by which the

dose is presented to the inhaler, a crank arm 2015 by which the dose blister (60-70) is pierced, a vortex nozzle 3000 for aerosolizing the dose, and an exit valve 2020 by which the aerosolized dose is released into the mouthpiece 10.

In use, the user places a foil blister (not shown) onto the blister loader 2010 and inserts the blister loader into the device in the position shown in Figure 23. The user then pierces the blister by moving the crank arm 2015 from a rest position to a pierce position in which it locks. The reservoir 80 is then charged from a compressed air line (not shown) such that the reservoir 80 contains a volume of pressurized air (typically 15ml) at a relatively low pressure (typically 1.5bar gauge). The compressed air is prevented from leaving the device by the valve 2020 at the exit to the vortex nozzle 3000. The device is now primed to deliver the dose.

When the user inhales via the mouthpiece, breath actuation vane 2025 moves, opening the exit valve 2020 and releasing the compressed air in the reservoir. The air flows through the blister, entraining the dose of powder and carrying it to the vortex nozzle 3000. In the nozzle the powder experiences high centrifugal and shear forces which deagglomerate the dose before delivering it to the user via the mouthpiece 10 as a finely dispersed aerosol.

Referring to Figure 25, the vortex nozzle 3000 comprises an inlet conduit 3, a vortex chamber 1, an outlet port 2 and a nozzle seal 3010. In use, the compressed gas and entrained dry powder dose from the blister (not shown) enters the vortex chamber via an inlet tube 7 and inlet conduit 3 and leaves the nozzle 3000 via the exit port 2. At the point 3020 where the inlet conduit 3 joins the vortex chamber 1, the outer wall of the chamber has a radius of 3.35mm. Continuing counter-clockwise along the wall of the chamber 1 for 180 degrees, the radius of the chamber reduces linearly to 2.5mm at point 3025. The radius is then constant at 2.5mm as the wall of the chamber continues in counter-clockwise direction until it intersects the inlet conduit. The height of the vortex chamber is 1.6mm. The inlet tube 7 has an internal diameter of 1.22mm and feeds into the inlet conduit 3.

The inlet conduit 3 tapers in section from a 1.22mm diameter where it joins the inlet tube 7 to its narrowest point where the inlet conduit 3 joins the vortex chamber 1 and has a height of 1.1mm high and a width of 0.5mm. As such, the inlet conduit 3 does not extend to the full height of the vortex chamber, which is 1.6 mm. The outlet port 2 diameter is 0.7mm and the thickness of the outlet port 2 is 0.35mm.

Referring to Figures 24, 26a and 26b, the breath actuated mechanism comprises a valve 2020 at the outlet port of the vortex nozzle, a valve spring 2030 biased to open the valve, a breath actuation vane 2040 that rotates in response to inhalation by a user, and an inspiratory air inlet 2035 through which air is drawn when a user inhales through the mouthpiece 10. The valve 2020 includes a resilient valve seal 2023 mounted on a valve arm 2022 which in turn is rotatably mounted on a valve arm pivot 2021. When the valve arm 2022 is in the closed position (Figure 26a), the valve seal 2023 covers and seals the vortex nozzle outlet port 2. In the open position (Figure 26b) the vortex nozzle outlet port 2 is open to allow the dose to exit the nozzle 3000.

The breath actuation vane 2040 is rotatably mounted on a vane pivot 2045. The vane 2040 includes a vane roller 2046 which is rotatably mounted on the vane 2045 and is free to rotate, and a vane return spring (not shown) which biases the vane 2040 to the closed position as shown in Figure 26a. When the valve 2040 is in the closed position, the valve seal 2023 is compressed to seal the nozzle outlet 2 and the opposite end of the valve arm 2022 rests on the vane roller 2046 and is prevented from rotating.

When a user inhales through the mouthpiece 10, air flows into the airway via the inspiratory air inlet 2035. This flow and the pressure drop it generates across the breath actuation vane 2040 cause the vane 2040 to rotate about its pivot 2045. The vane roller 2046 rolls against the end of the valve arm 2022 and then becomes clear of the valve arm 2022 as the vane 2040 rotates further. This allows the valve arm 2022 to rotate under the influence of the valve spring 2030, which removes the

valve seal 2023 from the output port 2 (i.e., opening the valve) to release the dose from the nozzle as shown in Figure 26b.

The breath actuated mechanism can be reset for the next dose by rotating the valve reset lever 2050 through 90 degrees and then returning it to its original position. The reset lever 2050 acts on the valve arm 2022 to close the valve (by causing the valve seal 2023 to cover output port 2) and allow the breath actuation vane 2040 to return to its closed position under the influence of the vane return spring (not shown).

Figure 27a shows a manually actuated mechanism in a closed position with a button 12 operably connected to the inspiratory air inlet 2035, constructed and arranged so that pushing the button 12 will cause the vane 2040 to rotate about its pivot 2045 and create an air flow in the same manner described above with reference to Figure 26a.

Figure 27b shows a manually actuated inhaler with the button 12 fully depressed and the inhaler in the open position as in Figure 26b. The manually actuated mechanism is reset in the same manner as the breath actuated mechanism, by rotating the valve reset lever 2050 through 90 degrees and then returning it to its original position.

In order to obtain the inhalation data described below, the inhaler of Figures 23 to 27 can be used in conjunction with three instruments, a Multi-Stage Liquid Impinger (MSLI) (U.S.P. 26, chapter 601, Apparatus 4 (2003), an Anderson Cascade Impactor (ACI) (U.S.P. 26, chapter 601, Apparatus 3 (2003), and a Dosage Unit Sampling Apparatus (DUSA) (U.S.P. 26 chapter 601, Apparatus B (2003). Each of these devices has an input for receiving the mouthpiece 10 of the inhaler of Figures 23 to 27.

The DUSA is used to measure the total amount of drug which leaves the inhaler. With data from this device, the metered and delivered dose is obtained. The delivered dose is defined as the amount of drug that leaves the inhaler. This includes the amount of drug in the throat of the DUSA device, in the measuring

section of the DUSA device and the subsequent filters of the DUSA device. It does not include drug left in the blister or other areas of the inhaler of Figures 23-27, and does not account for drug "lost" in the measuring process of the DUSA device. The metered does includes all of the drug which leaves the blister.

The MSLI is a device for estimating deep lung delivery of a dry powder formulation. The MSLI includes a five stage cascade impactor which can be used for determining the particle size (aerodynamic size distribution) of Dry Powder Inhalers (DPIs) in accordance with USP 26, Chapter 601 Apparatus 4 (2003).

The ACI is another device for estimating deep lung delivery of a dry powder formulation. The ACI is multi-stage cascade impactor which can be used for determining the particle size (aerodynamic size distribution) of Dry Powder Inhalers (DPI) in accordance with USP 26, Chapter 601 Apparatus 3 (2003).

The MSLI and the ACI testing devices can be used to determine, inter alia, the fine particle dose, or FPD (the amount of drug, e.g., in micrograms, that is measured in the sections of the testing device which correlates with deep lung delivery) and the fine particle fraction, or FPF, (the percentage of the metered dose which is measured in the sections of the testing device which correlates with deep lung delivery).

Example 4: Preparation of 3 milligram formulation with Magnesium Stearate in 4mg Blister

A 2 milligram formulation with magnesium stearate with the components provided in the following amounts:

Composition	Amount (µg)	Percent
Clobazam	3000	75.00
Lactose	990	24.75
Magnesium Stearate	10	00.25
Total	4000	100

This formulation is prepared in the manner set forth above with regard to Example 2, except that the magnesium stearate is added to the mixture along with the clobazam.

Example 5: Preparation of 4 milligram formulation with Leucine in 5mg Blister

A 4 milligram formulation with leucine with the components provided in the following amounts:

Composition	Amount (µg)	Percent
Clobazam	4000	80
Lactose	920	18
Micronised leucine	80	2
Total	5000	100

This formulation is prepared in the manner set forth above with regard to Example 2, except that the leucine is added to the mixture along with the clobazam.

Figure 28 shows the results of a particle size analysis of a preferred micronised leucine performed with the Mastersizer 2000, manufactured by Malvern Instruments, Ltd. (Malvern, UK). As illustrated, the exemplified micronised leucine has a volume weighted mean particle diameter of less than 6µm.

Example 6: Preparation of a 4mg Carrier-Free Formulation

A 4 milligram formulation with leucine with the components provided in the following amounts:

Composition	Amount (µg)	Percent
Clobazam	4000	99.9
Micronised Leucine	40.4	0.1
Total	4040.4	100

2g of the leucine described in Example 5 are mixed in a Turbula mixer with 198g of the clobazam powder described in Example 2. the resulting powder is agglomerated using a milling procedure. 50g samples of the powder were milled in a porcelain ball mill (manufactured by Pascall Engineering Company) having a diameter of

approximately 150mm, using steel grinding balls. 4040.4mg of the milled powder is then placed into each of 49 blisters.

Example 7: Comparison of Co-Jet Milled and Mechanofused Formulations (Clobozam)

Test Methods

All materials were evaluated in the Next Generation Impactor (NGI). Details of the test are provided in each case.

Formulations were processed using:

1) The Hosokawa Micron MechanoFusion AMS Mini system. This system was operated with a novel rotor, providing a 1mm compression gap; and

2) The Hosokawa Micron AS50 spiral jet mill.

The in-vitro testing was performed using an Aspirair (trade mark) device, which is an active inhaler device.

The formulations were composed of one or more of the following constituents:

Magnesium stearate (standard grade)

L-Leucine (Ajinomoto) and jet milled by Micron Technologies

Sorbolac 400 lactose

Micronised clobozam

Micronised lactose

Re-condensed Leucine (Aerocine)

The following is a comparison of 2-component systems comprising co-jet milled or mechanofused active particles and additive material.

1.01g of micronised clobozam was weighed out, and then gently pressed through a 300μm metal sieve, using the rounded face of a metal spatula. This formulation was recorded as "3A".

9.37g of micronised clobozam was then combined with 0.50g of micronised L-leucine in the MechanoFusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recorded as "4A". After blending, this powder was then gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "4B".

9.57g of micronised clobozam was then combined with 0.50g of magnesium stearate in the MechanoFusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recorded as "5A". After blending, this powder was rested overnight, and then was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "5B".

9.5g of micronised clobozam was then combined with 0.50g of micronised L-leucine in the MechanoFusion system. The material was processed at a relatively low speed setting of 20% power for 5 minutes. This process was intended only to produce a good mix of the components. This material was recorded as "6A".

6.09g of "6A" fed at approximately 1g per minute into an AS50 spiral jet mill, set with an injector pressure of about 7 bar and a grinding pressure of about 5 bar. The resulting material was recovered and recorded as "6B".

After milling, this powder was rested overnight, and then was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "6C".

9.5g of micronised clobozam was then combined with 0.50g of magnesium stearate in the MechanoFusion system. The material was processed at a setting of 20% power for 5 minutes. This material was recorded as "7A".

6.00g of "7A" was fed at approximately 1g per minute into the AS50 spiral jet mill, set with an injector pressure of about 7 bar and a grinding pressure of about 5 bar. The resulting material was recovered and recorded as "7B".

After milling, this powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "7C".

A batch of re-condensed leucine (also referred to as "Aerocine") was produced by subliming to vapour a sample of leucine in a tube furnace, and re-condensing as a very finely dispersed powder as the vapour cooled. This batch was identified as "8A".

9.5g of micronised clobozam was then combined with 0.50g of Aerocine, in the MechanoFusion system. The material was processed at a setting of 20% power for 5 minutes, followed by a setting of 80% power for 10 minutes. This material was recorded as "8B". After blending, this powder was rested overnight, and then was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "8C".

9.5g of micronised clobozam was combined with 0.50g of Aerocine in the MechanoFusion system. The material was processed at a setting of 20% power for 5 minutes. 7.00g of this powder was then fed into the AS50 spiral jet mill, set with an injector pressure of about 7 bar and a grinding pressure of about 5 bar. The resulting material was recovered and recorded as "9A".

After milling, this powder was gently pushed through a 300μm metal sieve with a spatula. This material was recorded as "9B".

A number of foil blisters were filled with approximately 2mg of the following clobozam formulations:

3A - no milling & no additive material

4B - leucine & mechanofused

5B - magnesium stearate & mechanofused

6C - leucine & co-jet milled

7C - magnesium stearate & co-jet milled

8C - Aerocine & co-jet milled

9B - Aerocine & mechanofused.

These formulations were then fired from an Aspirair device into an NGI at a flow rate of 60l/m. The Aspirair was operated under 2 conditions for each formulation: with a reservoir of 15ml of air at 1.5 bar or with a reservoir of 30ml of air at 0.5 bar.

The impactor test results are summarised in Tables 1, 2 and 3 below.

Table 1

Formulation	MD (mg)	ED (mg)	FPD(mg) (<5μm)	MMAD
3A 0.5 bar 30ml	2.04	1.12	0.88	2.91
3A 1.5 bar 15ml	1.92	1.74	1.23	2.86
4B 0.5 bar 30ml	1.84	1.48	0.82	3.84
4B 1.5 bar 15ml	1.80	1.56	0.81	3.32
5B 0.5 bar 30ml	1.84	1.53	1.17	2.34
5B 1.5 bar 15ml	1.85	1.55	1.12	2.22
6C 0.5 bar 30ml	1.93 1.86	1.80 1.73	1.67 1.62	2.11 2.11
6C 1.5 bar 15ml	1.97	1.86	1.67	2.07
6C 1.5 bar 15ml (silicon coated plates)	1.74	1.65	1.46	2.03
7C 0.5 bar 30ml	2.06	1.99	1.87	1.97
7C 1.5 bar 15ml	1.89	1.78	1.63	1.79
8C 0.5 bar 30ml	1.82	1.73	1.62	2.02
8C 1.5 bar 15ml	1.81	1.74	1.57	2.01
9B 0.5 bar 30ml	1.88	1.73	1.04	3.48
9B 1.5 bar 15ml	1.80	1.64	0.94	3.12

Table 2

Formulation	FPF(MD) % (<5μm)	FPF(ED) % (<5μm)	FPF(ED) % (<3μm)	FPF(ED) % (<2μm)	FPF(ED) % (<1μm)
3A 0.5 bar 30ml	43	78	49	32	17
3A 1.5 bar 15ml	64	71	45	24	6
4B 0.5 bar 30ml	45	55	28	15	7
4B 1.5 bar 15ml	45	52	30	18	9
5B 0.5bar 30ml	64	77	54	42	30
5B 1.5 bar 15ml	61	72	52	38	25
6C 0.5 bar 30ml	87 87	93 94	77 76	44 44	8 9
6C 1.5 bar 15ml	85	90	73	44	10
6C 1.5 bar 15ml (silicon coated plates)	84	89	74	45	8
7C 0.5 bar 30ml	91	94	79	50	14
7C 1.5 bar 15ml	86	92	82	56	16
8C 0.5 bar 30ml	89	93	79	48	12
8C 1.5 bar 15ml	87	90	76	46	9
9B 0.5 bar 30ml	55	60	34	24	15
9B 1.5 bar 15ml	52	57	34	24	15

Table 3

Formulation	*recovery	*throat	*blister	*device
3A 0.5 bar 30ml	102%	3%	1%	43%
3A 1.5 bar 15ml	96%	15%	1%	8%
4B 0.5 bar 30ml	97%	15%	7%	12%
4B 1.5 bar 15ml	95%	27%	6%	8%
5B 0.5 bar 30ml	97%	7%	13%	4%
5B 1.5 bar 15ml	98%	14%	12%	4%
6C 0.5 bar 30ml	97% 101%	2% 3%	1% 1%	6% 5%
6C 1.5 bar 15ml	104%	6%	3%	3%
6C 1.5 bar 15ml (silicon coated plates)	91%	8%	1%	4%
7C 0.5 bar 30ml	110%	2%	1%	3%
7C 1.5 bar 15ml	99%	6%	2%	3%
8C 0.5 bar 30ml	99%	3%	1%	4%
8C 1.5 bar 15ml	95%	6%	1%	3%
9B 0.5 bar 30ml	96%	16%	2%	7%
9B 1.5 bar 15ml	95%	26%	4%	5%

From these results it can be seen that the co-jet milled formulations exhibited exceptional FPFs when dispensed from an active dry powder inhaler device. The FPFs observed were significantly better that those of the mechanofused formulations and those formulations which did not include an additive material. This improvement would appear to be largely due to reduced throat deposition, which was less than 8% for the co-jet milled formulations, compared to 15% for the pure drug and up to 27% for the mechanofused formulations.

The reproducibility of the FPFs obtained was also tested. Through life dose uniformity for the primary candidate, 6C, the preparation of which is described above, was tested by firing 30 doses, with the emitted doses collected by DUSA.

The mean ED was 1965μg, with an RSD (relative standard deviation) of 2.8%. This material consequently demonstrated excellent through life dose reproducibility.

Example 8 - Preparation of pMDI formulation

A further composition according to the present invention may be prepared as follows. 12.0g micronised benzodiazepine, such as clobozam, and 4.0g lecithin S PC-3 (Lipoid GMBH) are weighed into a beaker. The powder is transferred to the Hosokawa AMS-MINI MechanoFusion system via a funnel attached to the largest port in the lid with the equipment running at 3.5%. The port is sealed and the cooling water switched on. The equipment is run at 20% for 5 minutes followed by 50% for 10 minutes. The equipment is switched off, dismantled and the resulting formulation recovered mechanically.

Preparation of cans:

0.027g powder is weighed into the can, a 50μl valve is crimped to the can and 12.2g HFA 134a is back filled into the can.

Example 9- Preparation of MechanoFused formulation for use in passive device

A further composition according to the present invention may be prepared as follows. 20g of a mix comprising 20% micronised benzodiazepine, such as clobozam, 78% Sorbolac 400 lactose and 2% magnesium stearate are weighed into the Hosokawa AMS-MINI MechanoFusion system via a funnel attached to the largest port in the lid with the equipment running at 3.5%. The port is sealed and the cooling water switched on. The equipment is run at 20% for 5 minutes followed by 80% for 10 minutes. The equipment is switched off, dismantled and the resulting formulation recovered mechanically.

Example 10- Preparation of two step MechanoFused formulation for use in passive device

A further composition according to the present invention may be prepared as follows. In Stage 1, 20g of a mix comprising 95% micronised benzodiazepine, such as clobozam, and 5% magnesium stearate are weighed into the Hosokawa AMS-MINI MechanoFusion system via a funnel attached to the largest port in the lid with the equipment running at 3.5%. The port is sealed and the cooling water switched on. The equipment is run at 20% for 5 minutes followed by 80% for 10 minutes. The equipment is switched off, dismantled and the resulting powder recovered mechanically. In stage 2, 20g of a mix comprising 99% Sorbolac 400 lactose and 1% magnesium stearate are weighed into the Hosokawa AMS-MINI MechanoFusion system via a funnel attached to the largest port in the lid with the equipment running at 3.5%. The port is sealed and the cooling water switched on. The equipment is run at 20% for 5 minutes followed by 80% for 10 minutes. The equipment is switched off, dismantled and the resulting powder recovered mechanically. Following this, 16g of powder from stage 2 are combined with 4g of powder from stage 1 in a small high shear blender, for 10 minutes to produce the formulation.